



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12Q 1/68, G01N 33/574	A3	(11) International Publication Number: WO 98/53319 (43) International Publication Date: 26 November 1998 (26.11.98)
(21) International Application Number: PCT/US98/10277 (22) International Filing Date: 20 May 1998 (20.05.98) (30) Priority Data: 60/047,352 21 May 1997 (21.05.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/047,352 (CON) Filed on 21 May 1997 (21.05.97) (71) Applicant (for all designated States except US): THE JOHNS HOPKINS UNIVERSITY [US/US]; Suite 2-100, 2024 E. Monument Street, Baltimore, MD 21205 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): VOGELSTEIN, Bert [US/US]; The Johns Hopkins University, Suite 2-100, 2024 E. Monument Street, Baltimore, MD 21205 (US). KINZLER, Kenneth, W. [US/US]; The Johns Hopkins University, Suite 2-100, 2024 E. Monument Street, Baltimore, MD 21205 (US).	(74) Agents: KAGAN, Sarah, A. et al.; Banner & Witcoff, Ltd., 11th floor, 1001 G Street, N.W., Washington, DC 20001-4597 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 8 July 1999 (08.07.99)	
(54) Title: GENE EXPRESSION PROFILES IN NORMAL AND CANCER CELLS (57) Abstract As a step towards understanding the complex differences between normal and cancer cells, gene expression patterns were examined in gastrointestinal tumors. More than 300,000 transcripts derived from at least 45,000 different genes were analyzed. Although extensive similarity was noted between the expression profiles, more than 500 transcripts that were expressed at significantly different levels in normal and neoplastic cells were identified. These data provide insights into the extent of expression differences underlying malignancy and reveal genes that are useful as diagnostic or prognostic markers.		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/10277

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C12Q1/68 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUGIO K ET AL.: "Differential expression of c-myc gene and c-fos gene in premalignant and malignant tissues." CANCER RESEARCH, vol. 48, no. 17, 1988, pages 4855-4861, XP002089885 see the whole document	1,3,13, 16,17,28
X	VAN BELZEN N ET AL.: "Detection of different gene expression in differentiating colon carcinoma cells by differential display" JOURNAL OF PATHOLOGY, vol. 178, no. Suppl., - 1996 page 2A XP002089886 see abstract	1,3,5,7, 9,11
Y	---	26,28,34
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

13 January 1999

Date of mailing of the international search report

24 05. 1999

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/10277

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 21944 A (SMITHKLINE BEECHAM CORP ;ROSENBERG MARTIN (US); DEBOUCK CHRISTINE) 17 August 1995 see the whole document ---	26,28,34
Y	EP 0 284 362 A (ICI PLC) 28 September 1988 see abstract see page 2, line 44 - line 51 see page 10, line 12 - line 15; claims 1,9; figure 2 ---	1,3,5,7, 9,11, 13-23, 26,28, 34,52
Y	EP 0 761 822 A (UNIV JOHNS HOPKINS MED) 12 March 1997 see the whole document ---	1,3,5,7, 9,11, 13-23, 26,28, 34,52
Y	WO 95 11923 A (DANA FARBER CANCER INST INC ;CHEN LAN BO (US); BAO SHIDENG (CN); L) 4 May 1995 see the whole document ---	1,3,5,7, 9,11, 13-18, 23,26, 28,34,52
Y	VELCULESCU V E ET AL.: "SERIAL ANALYSIS OF GENE EXPRESSION" SCIENCE, vol. 270, 20 October 1995, pages 484-487, XP002053721 cited in the application see the whole document ---	1,3,5,7, 9,11, 13-18, 23,26, 28,34,52
Y	SCHWEINFEST C W ET AL.: "Subtraction hybridization cDNA libraries from colon carcinoma and hepatic cancer" GENETIC ANALYSIS TECHNIQUES AND APPLICATIONS, vol. 7, 1990, pages 64-70, XP002089887 see the whole document ---	1,3,5,7, 9,11, 13-18, 23,26
Y	WO 97 14812 A (CHIRON CORP) 24 April 1997 see the whole document ---	52
A	GRESS T M ET AL.: "A pancreatic cancer-specific expression profile" ONCOGENE, vol. 13, 1996, pages 1819-1830, XP002089888 see the whole document ---	

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/10277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 19369 A (UNIV VANDERBILT) 20 July 1995 see the whole document	
A	--- GRESS T ET AL.: "Identification of genes with pancreatic cancer specific expression by use of cDNA representational difference analysis" GASTROENTEROLOGY, vol. 110, no. 4 Suppl., 1996, XP002089889 see abstract	
P,X	--- ZHANG L E AL.: "Gene expression profiles in normal and cancer cells." SCIENCE, vol. 276, 1997, pages 1268-1272, XP002089890 see the whole document	1,3,5,7, 9,11, 13-23, 26,28, 34,52
P,X	--- VAN BELZEN N ET AL.: "A novel gene which is up-regulated during colon epithelial cell differentiation and down-regulated in colorectal neoplasms" LABORATORY INVESTIGATION, vol. 77, no. 1, 1997, pages 85-92, XP002089891 see the whole document -----	1,3,5,7, 9,11,13, 14, 16-18, 23,26, 28,34

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 10277

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see FURTHER INFORMATION sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see FURTHER INFORMATION sheet, subject 1.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 98/10277

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,3,5,7,9,11,13-23,26,28,34,52 (partial)

INVENTION 1:

An isolated and purified human nucleic acid molecule comprising SEQ ID NO:291 of table 3 (INVENTION 1), an isolated nucleotide probe hybridizing to it, a diagnostic reagent comprising at least two of such probes, methods of diagnosing or prognosing colon cancer using them, and a method for screening for agents modulating the expression of such a sequence using them.

2. Claims: 1,3,5,7,9,11,13-23,26,28,34,52 (partial)

INVENTION 2 to INVENTION 259:

An isolated and purified human nucleic acid molecule comprising SEQ ID NO:292 of table 3 (INVENTION 2), an isolated nucleotide probe hybridizing to it, a diagnostic reagent comprising at least two of such probes, methods of diagnosing or prognosing colon cancer using them, and a method for screening for agents modulating the expression of such a sequence using them.

...ibidem for each of the SEQ ID Nos:293 to 549 (INVENTION 3 to INVENTION 259) as specified in table 3, separately.

3. Claims: 2,4,6,8,10,12-23,27,29,35,38-40,43,46,49, 52 (partial)

INVENTION 260 to INVENTION 549:

An isolated and purified human nucleic acid molecule comprising SEQ ID NO:1 of table 2 (INVENTION 260), an isolated nucleotide probe hybridizing to it, a diagnostic reagent comprising at least two of such probes, methods of diagnosing or prognosing colon cancer using them, a method of treating a cancer cell using them, an antibody linked to a cytotoxic agent used in such a method, and a method for screening for agents modulating the expression of such a sequence using them.

...ibidem for each of the SEQ ID Nos:2 to 290 (INVENTION 261 to INVENTION 549) as specified in table 2, separately.

4. Claims: 13-24,30,32,36,38,39,41,44,47,50,52 (partial)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ US 98/10277

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

INVENTION 550 to INVENTION 732:

An isolated and purified human nucleic acid molecule comprising SEQ ID NO:550 of table 4 (INVENTION 550), an isolated nucleotide probe hybridizing to it, a diagnostic reagent comprising at least two of such probes, methods of diagnosing or prognosing pancreatic cancer using them, a method of treating a cancer cell using them, an antibody linked to a cytotoxic agent used in such a method, and a method for screening for agents modulating the expression of such a sequence using them.

...ibidem for each of the SEQ ID Nos:551 to 732 (INVENTION 551 to INVENTION 732) as specified in table 4, separately.

5. Claims: 24,30,32,36,38,39,41,44,47,50 (partial)

INVENTION 733 to INVENTION 734:

Methods of diagnosing or prognosing pancreatic cancer relying on a human nucleic acid molecule comprising SEQ ID NO:733 of table 4 (INVENTION 733), a method of treating a cancer cell using it, and an antibody linked to a cytotoxic agent used in such a method.

...ibidem for SEQ ID Nos:734 (INVENTION 734) as specified in table 4.

6. Claims: 25,31,33,37-39,42,45,48,51 (partial)

INVENTION 735 to INVENTION 870:

Methods of diagnosing or prognosing cancer relying on a human nucleic acid molecule comprising SEQ ID NO:735 of table 5 (INVENTION 735), a method of treating a cancer cell using it, and an antibody linked to a cytotoxic agent used in such a method.

...ibidem for each of the SEQ ID Nos:736 to 870 (INVENTION 736 to INVENTION 870) as specified in table 5, separately.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/10277

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521944 A	17-08-1995	EP 0743989 A JP 9508800 T	27-11-1996 09-09-1997
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